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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
CROUCH, DEBORAH

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/708,096	WONG ET AL.	
	Examiner	Art Unit	
	Deborah Crouch	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-69 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-69 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-3 and 5, drawn to a method for modulating production of Aβ11-40/42 peptide fragments comprising contacting a sample or cell in vivo containing BACE1 and an APP with a BACE1-modulating agent where the modulating agent is a BACE1 antibody, classified in class 424, subclass 9.1.

II. Claims 1-3 and 5, drawn to drawn to a method for modulating production of Aβ11-40/42 peptide fragments comprising contacting a sample or cell in vivo containing BACE1 and an APP with a BACE1-modulating agent where the modulating agent is a BACE1 antisense molecule, classified in class 424, subclass 9.1.

III. Claims 1,2,4 and 5, drawn to a method for modulating production of Aβ11-40/42 peptide fragments comprising contacting a sample or cell in vitro containing BACE1 and an APP with a BACE1-modulating agent where the modulating agent is a BACE1 antibody, classified in class 435, subclass 29.

IV. Claims 1,2,4 and 5, drawn to a method for modulating production of Aβ11-40/42 peptide fragments comprising contacting a sample or cell in vitro containing BACE1 and an APP with a BACE1-modulating agent where the modulating agent is a BACE1 antisense molecule, classified in class 435, subclass 29.

V. Claims 6,7,9 and 10, drawn to a method for identifying a compound that inhibits BACE1 expression or activity comprising incubating a peptide compound and a BACE1 polynucleotide, classified in class 435, subclass 23.

VI. Claims 6,7,9 and 10, drawn to a method for identifying a compound that inhibits BACE1 expression or activity comprising incubating a peptide compound and a BACE1 polypeptide, classified in class 435, subclass 23.

VII. Claims 6, and 8-10 drawn to a method for identifying a compound that inhibits BACE1 expression or activity comprising incubating a small molecule compound and a BACE1 polynucleotide, classified in class 435, subclass 23.

VIII. Claims 6, and 8-10 drawn to a method for identifying a compound that inhibits BACE1 expression or activity comprising incubating a small molecule compound and a BACE1 polypeptide, classified in class 435, subclass 23.

IX. Claim 11, drawn to composition, not classifiable.

X. Claim 12, drawn to composition in a pharmaceutically acceptable carrier, not classifiable.

XI. Claims 13-18, drawn to a method for diagnosing a subject having or at risk for having an Aβ11-40/42 peptide accumulation disease comprising measuring the level of BACE1 in a biological sample measuring the amount of a polynucleotide encoding BACE1, classified in class 435, subclass 6.

XII. Claims 13-15 and 19-23, drawn to a method for diagnosing a subject having or at risk for having an Aβ11-40/42 peptide accumulation disease comprising measuring the level of BACE1 in a biological sample using an antibody, classified in class 435, subclass 7.1.

XIII. Claims 13, and 24-29, drawn to a method for diagnosing a subject having or at risk for having an Aβ11-40/42 peptide accumulation disease comprising measuring the level of BACE1 in a biological sample measuring, and further comprising detecting the level of an APP by antibody binding, classified in class 435, subclass 7.1.

XIV Claims 30-38, 40 and 41, drawn to a method for diagnosing a subject having or at risk for having Alzheimer's Disease comprising measuring the level of

Aβ11-40/42 in a biological sample measuring by antibody binding, classified in class 435, subclass 7.1.

XV Claims 30 and 39, drawn to a method for diagnosing a subject having or at risk for having Alzheimer's Disease comprising measuring the level of Aβ11-40/42 in a biological sample measuring by antibody binding, and further comprising detecting the level of a BACE1 polypeptide, classified in class 435, subclass 23.

XVI Claims 30 and 39, drawn to a method for diagnosing a subject having or at risk for having Alzheimer's Disease comprising measuring the level of Aβ11-40/42 in a biological sample measuring by antibody binding, and further comprising detecting the level of a BACE1 polynucleotide, classified in class 435, subclass 6.

XVII. Claims 42-64, drawn to nonhuman transgenic animals having a disruption of a BACE1 gene where the animals exhibit reduced Aβ peptide, methods of producing the animals, and methods for using the animal in assay systems to determine agents that modulate expression or activity of BACE1, and methods of screening agents that ameliorate symptoms of Alzheimer's Disease, classified in class 800, subclass 3, as an example.

XVIII. Claims 65-67, drawn to a kit comprising a nucleic acid probe that hybridizes to a nucleic acid sequence BACE1, classified in class 536, subclass 24.3

XIX. Claims 65-67, drawn to a kit comprising an antibody specific for BACE1, classified in class 530, subclass 387.1.

XX. Claim 68, drawn to a method for predicting the therapeutic effectiveness of a compound for treating Alzheimer's disease comprising measuring the

accumulation Aβ11-40/42 peptide fragments before and after administering the compound, classified in class 435, subclass 7.1.

XXI. Claim 68, drawn to a method for predicting the therapeutic effectiveness of a compound for treating Alzheimer's disease comprising measuring the level of BACE1 polynucleotide before and after administering the compound, classified in class 435, subclass 6.

XXII. Claim 68, drawn to a method for predicting the therapeutic effectiveness of a compound for treating Alzheimer's disease comprising measuring the level of BACE1 polypeptide before and after administering the compound, classified in class 435, subclass 23.

XXIII. Claim 69, drawn to a method for monitoring the progression of Alzheimer's disease comprising measuring the accumulation Aβ11-40/42 peptide fragments, classified in class 435, subclass 7.1.

XXIV. Claim 69, drawn to drawn to a method for monitoring the progression of Alzheimer's disease comprising measuring the level of BACE1 polynucleotide, classified in class 435, subclass 6.

XXV. Claim 69, drawn to a method for monitoring the progression of Alzheimer's disease comprising measuring the level of BACE1 polypeptide, classified in class 435, subclass 23.

The inventions are distinct, each from the other because:

Inventions I and II are mutually exclusive and independent methods for modulating the production of Aβ11-40/42 in vivo as the active agent in invention I is an antibody, and the active agent in invention II is an antisense molecule. Antibodies and antisense molecules are of separate mode of action. Further, neither method is required for the implementation of the other method.

Inventions I, and inventions III and IV are mutually exclusive and independent methods for modulating the production of Aβ11-40/42. Invention I is an in vivo method where the antibody is administered to an animal whereas Inventions III and IV are in vitro methods, where the antibody or antisense molecule is delivered to an assay system that does not require an animal. Further, neither method is required for the implementation of the other method.

Invention I, and inventions V-VIII are mutually exclusive and independent methods as the assay end-points are materially different and separate. Invention I requires that the modulation of Aβ11-40/42 be determined whereas each of inventions V-VIII require that the inhibition of BACE1 expression be determined. Further, neither method is required for the implementation of any of the other methods.

Invention I, and inventions IX and X are mutually exclusive and independent. The method of invention I is not needed to implement the compositions of inventions IX and X, and vice versa.

Invention I, and inventions XI-XVI are mutually exclusive and independent methods. The method of invention I is to a method for modulating the production of Aβ11-40/42 in vivo where the active agent in invention I is an antibody. The methods of inventions XI-XVI are to methods of diagnosing a risk for having an Aβ11-40/42 accumulating disease. The end-points for the two types of methods is materially different and separate as are the protocols for achieving such. Further, invention I is not needed to implement any of inventions XI-XVI, and vice versa.

Invention I and invention XVII are mutually exclusive and independent. The method of modulating of Invention I is not needed for the transgenic nonhuman

animal invention XVII. The protocols for invention I and XVII are materially different and separate.

Inventions I and XVIII are materially different and separate. The method of modulating of invention I is not required for the implementation of the nucleic acid probe of invention XVIII, and vice versa.

Inventions I and XIX are related as process of use and product. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the kit of invention XVIX can be used in immuno-purification procedures.

Inventions I, and XX-XXII are mutually exclusive and independent methods. Invention I is to methods of in vivo modulation of Aβ1-40/42 production. Inventions XX-XXII are to a method of predicting the therapeutic effectiveness of a compound for treating Alzheimer's disease by determining the accumulation of Aβ1-40/42 fragments. As the assay endpoints are materially different and separate in inventions I, and XX-XXII, they would require materially different and separate protocols. Further, neither method is need for the implementation of the other method.

Inventions I, and XXIII-XXV are mutually exclusive and independent methods. Invention I is to methods of in vivo modulation of Aβ1-40/42 production. Inventions XXIII-XXV are to a method of monitoring the progression of Alzheimer's disease comprising measuring the accumulation of Aβ1-40/42 fragments. As the assay endpoints are materially different and separate in inventions I, and XX-XXII, they would require materially different and separate protocols. Further, neither method is need for the implementation of the other method.

Inventions II, and inventions III and IV are mutually exclusive and independent methods for modulating the production of Aβ11-40/42. Invention II is an in vivo method where the antisense molecule is administered to an animal whereas Inventions III and IV are in vitro methods, where the antibody or antisense molecule is delivered to an assay system that does not require an animal. Further, neither method is required for the implementation of the other method.

Invention II, and inventions V-VIII are mutually exclusive and independent methods as the assay end-points are materially different and separate. Invention II requires that the modulation of Aβ11-40/42 be determined whereas each of inventions V-VIII require that the inhibition of BACE1 expression be determined. Further, neither method is required for the implementation of any of the other methods.

Invention II, and inventions IX and X are mutually exclusive and independent. The method of invention II is not needed to implement the compositions of inventions IX and X, and vice versa.

Invention II, and inventions XI-XVI are mutually exclusive and independent methods. The method of invention II is to a method for modulating the production of Aβ11-40/42 in vivo where the active agent in invention II is an antisense molecule. The methods of inventions XI-XVI are to methods of diagnosing a risk for having an Aβ11-40/42 accumulating disease. The end-points for the two types of methods is materially different and separate as are the protocols for achieving such. Further, invention II is not needed to implement any of inventions XI-XVI, and vice versa.

Invention II and Invention XVII are mutually exclusive and independent. The method of modulating of Invention II is not needed for the transgenic nonhuman

animal invention XVII. The protocols for invention II and XVII are materially different and separate.

Inventions II and XVIII are related as process of use and product. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the kit of invention XVIII can be used to isolate a gene for BACE1.

Inventions II and XIX are materially different and separate. The method of modulating of invention II is not required for the implementation of the antibody of invention XIX, and vice versa.

Inventions II, and XX-XXII are mutually exclusive and independent methods. Invention II is to a method of in vivo modulation of Aβ1-40/42 production. Inventions XX-XXII are to a method of predicting the therapeutic effectiveness of a compound for treating Alzheimer's disease by determining the accumulation of Aβ1-40/42 fragments. As the assay endpoints are materially different and separate in inventions II, and XX-XXII, they would require materially different and separate protocols. Further, neither method is need for the implementation of the other method.

Inventions II, and XXIII-XXV are mutually exclusive and independent methods. Invention II is to methods of in vivo modulation of Aβ1-40/42 production. Inventions XXIII-XXV are to a method of monitoring the progression of Alzheimer's disease comprising measuring the accumulation of Aβ1-40/42 fragments. As the assay endpoints are materially different and separate in inventions II, and XX-XXII,

they would require materially different and separate protocols. Further, neither method is need for the implementation of the other method.

Inventions III and IV are mutually exclusive and independent methods for modulating the production of Aβ11-40/42. Invention III is an in vitro method where an antibody is delivered to an assay system that does not require an animal. Invention IV is an in vitro method where an antisense molecule is delivered to an assay system that does not require an animal. Further, neither method is required for the implementation of the other method.

Invention III, and inventions V-VIII are mutually exclusive and independent methods as the assay end-points are materially different and separate. Invention III requires that the modulation of Aβ11-40/42 be determined whereas each of inventions V-VIII require that the inhibition of BACE1 expression be determined. Further, neither method is required for the implementation of any of the other methods.

Invention III, and inventions IX and X are mutually exclusive and independent. The method of invention III is not needed to implement the compositions of inventions IX and X, and vice versa.

Invention III, and inventions XI-XVI are mutually exclusive and independent methods. The method of invention III is to a method for modulating the production of Aβ11-40/42 in vivo where the active agent in invention III is an antibody molecule. The methods of inventions XI-XVI are to methods of diagnosing a risk for having an Aβ11-40/42 accumulating disease. The end-points for the two types of methods is materially different and separate as are the protocols for achieving such. Further, invention III is not needed to implement any of inventions XI-XVI, and vice versa.

Invention III and Invention XVII are mutually exclusive and independent. The method of modulating of Invention III is not needed for the transgenic nonhuman animal invention XVII. The protocols for invention III and XVII are materially different and separate.

Inventions III and XVIII are materially different and separate. The method of modulating of invention III is not required for the implementation of the nucleic acid probe of invention XVIII, and vice versa.

Inventions III and XIX are related as process of use and product. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the kit of invention XVIX can be used in immuno-purification procedures.

Inventions III, and XX-XXII are mutually exclusive and independent methods. Invention III is to a method of in vivo modulation of Aβ1-40/42 production. Inventions XX-XXII are to a method of predicting the therapeutic effectiveness of a compound for treating Alzheimer's disease by determining the accumulation of Aβ1-40/42 fragments. As the assay endpoints are materially different and separate in inventions III, and XX-XXII, they would require materially different and separate protocols. Further, neither method is need for the implementation of the other method.

Inventions III, and XXIII-XXV are mutually exclusive and independent methods. Invention III is to methods of in vivo modulation of Aβ1-40/42 production. Inventions XXIII-XXV are to a method of monitoring the progression of Alzheimer's disease comprising measuring the accumulation of Aβ1-40/42 fragments. As the

assay endpoints are materially different and separate in inventions III, and XX-XXII, they would require materially different and separate protocols. Further, neither method is need for the implementation of the other method.

Invention IV, and inventions V-VIII are mutually exclusive and independent methods as the assay end-points are materially different and separate. Invention IV requires that the modulation of Aβ11-40/42 be determined whereas each of inventions V-VIII require that the inhibition of BACE1 expression be determined. Further, neither method is required for the implementation of any of the other methods.

Invention IV and inventions IX and X are mutually exclusive and independent. The method of invention IV is not needed to implement the compositions of inventions IX and X, and vice versa.

Invention IV, and inventions XI-XVI are mutually exclusive and independent methods. The method of invention IV is to a method for modulating the production of Aβ11-40/42 in vivo where the active agent in invention IV is an antisense molecule. The methods of inventions XI-XVI are to methods of diagnosing a risk for having an Aβ11-40/42 accumulating disease. The end-points for the two types of methods is materially different and separate as are the protocols for achieving such. Further, invention IV is not needed to implement any of inventions XI-XVI, and vice versa.

Invention IV and Invention XVII are mutually exclusive and independent. The method of modulating of Invention IV is not needed for the transgenic nonhuman animal invention XVII. The protocols for invention IV and XVII are materially different and separate.

Invention IV and XVIII are related as process of use and product. The inventions can be shown to be distinct if either or both of the following can be

shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the kit of invention XVIII can be used to isolate a gene for BACE1.

Inventions IV and XIX are materially different and separate. The method of modulating of invention IV is not required for the implementation of the antibody of invention XIX, and vice versa.

Inventions IV, and XX-XXII are mutually exclusive and independent methods. Invention IV is to a method of in vivo modulation of Aβ1-40/42 production. Inventions XX-XXII are to a method of predicting the therapeutic effectiveness of a compound for treating Alzheimer's disease by determining the accumulation of Aβ1-40/42 fragments. As the assay endpoints are materially different and separate in inventions IV, and XX-XXII, they would require materially different and separate protocols. Further, neither method is need for the implementation of the other method.

Inventions IV, and XXIII-XXV are mutually exclusive and independent methods. Invention IV is to a method of in vivo modulation of Aβ1-40/42 production. Inventions XXIII-XXV are to a method of monitoring the progression of Alzheimer's disease comprising measuring the accumulation of Aβ1-40/42 fragments. As the assay endpoints are materially different and separate in inventions IV, and XX-XXII, they would require materially different and separate protocols. Further, neither method is need for the implementation of the other method.

Inventions V-VIII are mutually exclusive and independent methods for identifying a compound that inhibits BACE1 expression or activity comprising determining the effect of a peptide or a small molecule on either BACE1

polynucleotide or polypeptide. Each combination of compound and assay end-point are materially different and separate in assay protocols and data analysis. As the four combinations are materially different and separate from each other, neither method is needed for the implementation of any of the other methods.

Inventions V-VIII and inventions IX and X are distinct. The methods of V-VIII can be used to identify large molecules that inhibit BACE1 expression or activity.

Inventions V-VIII and, and inventions XI-XVI are mutually exclusive and independent methods. Inventions V-VIII are methods for identifying a compound that inhibits BACE1 expression or activity comprising determining the effect of a peptide or a small molecule on either BACE1 polynucleotide or polypeptide. Inventions XI-XVI are to methods of diagnosing a risk for having an Aβ11-40/42 accumulating disease. The end-points for the two types of methods are materially different and separate as are the protocols for achieving such. Further, inventions V-VIII is not needed to implement any of inventions XI-XVI, and vice versa.

Inventions V-VIII and Invention XVII are mutually exclusive and independent. The methods for identifying of inventions V-VIII are not needed for the transgenic nonhuman animal invention XVII. The protocols for inventions V-VIII and XVII are materially different and separate.

Inventions V-VIII and XVIII are related as process of use and product. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the kit of invention XVIII can be used to isolate a gene for BACE1.

Inventions V-VIII and XIX are materially different and separate. The method of identifying compounds of invention IV is not required for the implementation of the antibody of invention XIX, and vice versa.

Inventions V-VIII, and XX-XXII are mutually exclusive and independent methods. Inventions V-VIII are methods for identifying a compound that inhibits BACE1 expression or activity comprising determining the effect of a peptide or a small molecule on either BACE1 polynucleotide or polypeptide. Inventions XX-XXII are to a method of predicting the therapeutic effectiveness of a compound for treating Alzheimer's disease by determining the accumulation of Aβ1-40/42 fragments. As the assay endpoints are materially different and separate in inventions V-VIII, and XX-XXII, they would require materially different and separate protocols. Further, neither method is need for the implementation of the other method.

Inventions V-VIII, and XXIII-XXV are mutually exclusive and independent methods. Invention IV is to a method of in vivo modulation of Aβ1-40/42 production. Inventions XXIII-XXV are to a method of monitoring the progression of Alzheimer's disease comprising measuring the accumulation of Aβ1-40/42 fragments. As the assay endpoints are materially different and separate in inventions IV, and XX-XXII, they would require materially different and separate protocols. Further, neither method is need for the implementation of the other method.

Inventions IX and X are distinct inventions as they are capable of separate uses. The composition of invention IX can be used in in vitro assays, and the pharmaceutical composition can be used in in vivo assays.

Inventions IX and X, and inventions XI-XVI are mutually exclusive. The compositions of inventions IX and X are not needed for the implementation of inventions XI-XVI to methods of for diagnosing.

Inventions IX and X, and invention XVII are mutually exclusive and independent. The compositions of inventions IX and X are not needed for the transgenic nonhuman animal invention XVII, and vice-versa.

Inventions IX and X, and invention XVIII are mutually exclusive and independent. The compositions of inventions IX and X are not needed for the nucleic acid probe of invention XVIII, and vice versa.

Inventions IX and X, and XIX are mutually exclusive and independent. The compositions of inventions IX and X are not needed for the antibody of invention XIX, and vice versa.

Inventions IX and X, and XX-XXII are mutually exclusive and independent. The compositions of inventions X and XI are not needed for inventions XX-XXII, to a method of predicting the therapeutic effectiveness of a compound for treating Alzheimer's disease by determining the accumulation of Aβ1-40/42 fragments, and vice-versa.

Inventions IX and X, and XXIII-XXV are mutually exclusive and independent. The compositions of inventions X and XI are not needed to implement inventions XXIII-XXV, to a method of monitoring the progression of Alzheimer's disease comprising measuring the accumulation of Aβ11-40/42 fragments, and vice versa.

Inventions XI-XVI are mutually exclusive and independent methods of diagnosing a subject having or at risk for having an Aβ11-40/42 accumulation disease comprising measuring the levels of BACE1 and methods of diagnosing a subject having or at risk for having Alzheimer's disease comprising measuring the level of Aβ11-40/42 where the levels of BACE1 or Aβ11-40/42 is by antibodies or the level of BACE or Aβ11-40/42 polynucleotide is determined. The methods are mutually exclusive and independent, as the methods require materially different and separate

protocols and the measuring of separate endpoints. Further, none of the methods of XI-XVI are required for the implementation of any of the other methods contained therein.

Inventions XI-XVI and invention XVII are mutually exclusive and independent. Inventions XI-XVI are methods of diagnosing a subject having or at risk for having an Aβ11-40/42 accumulation disease comprising measuring the levels of BACE1 and methods of diagnosing a subject having or at risk for having Alzheimer's disease comprising measuring the level of Aβ11-40/42. Invention XVII is to transgenic nonhuman animals. None of the methods of XI-XVI are required for the implementation of the invention of XVII, and vice-versa.

Inventions XI, XIII and XVI, and invention XVIII are related as process of use and product. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the kit of invention XVIII can be used to isolate a gene for BACE1.

Inventions XII, XIII, XIV and XV, and invention XVIII are mutually exclusive and independent. None of the methods of XII, XIII, XIV and XV require the nucleic acid of invention XVIII and vice versa.

Inventions XI and XIII-XVI, and invention XIX are mutually exclusive and independent. The methods of inventions XI and XIII-XVI do not require the antibody of invention XIX, and vice versa.

Inventions XII and XIX are related as process of use and product. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with

another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the antibody of invention XIX can be used in immune-purification procedures.

Inventions XI-XVI, and XX-XXII are mutually exclusive and independent methods. Inventions XI-XVI are methods of diagnosing a subject having or at risk for having an Aβ11-40/42 accumulation disease comprising measuring the levels of BACE1 and methods of diagnosing a subject having or at risk for having Alzheimer's disease comprising measuring the level of Aβ11-40/42. Inventions XX-XXII are to a method of predicting the therapeutic effectiveness of a compound for treating Alzheimer's disease by determining the accumulation of Aβ1-40/42 fragments. The protocols for the assays of inventions XI-XVI and XX-XXII are materially different and separate. Further, neither method is need for the implementation of the other method.

Inventions XI-XVI, and XXIII-XXV are mutually exclusive and independent methods. Inventions XI-XVI are methods of diagnosing a subject having or at risk for having an Aβ11-40/42 accumulation disease comprising measuring the levels of BACE1 and methods of diagnosing a subject having or at risk for having Alzheimer's disease comprising measuring the level of Aβ11-40/42. The protocols for the assays in inventions XI-XVI and inventions XXIII-XXV are materially different and separate. Further, neither method is need for the implementation of the other method.

Invention XVII, and inventions XVII and XIX are mutually exclusive and independent. Invention XVII is to a transgenic nonhuman animal. Invention XVII is to a kit comprising a nucleic acid probe, and invention XIX is to a kit comprising an antibody probe. Invention XVII, inventions XVII and XIX are not need for the implementation of each other.

Invention XVII, and the inventions of any of inventions XX-XXV are mutually exclusive and independent. The transgenic animal of invention XVII is not required for the implementation of any of the methods in any invention of XX-XXV.

Invention XVIII, and invention XIX are mutually exclusive and independent. The kit of invention XVIII comprising a polynucleotide is not required for the implementation of the kit of invention XIX, comprising an antibody.

Invention XVIII, and any of inventions XX, XXIII and XXV are mutually exclusive and independent. The kit comprising a nucleic acid probe of invention XVII is not needed for the implementation of any of inventions XX, XXIII and XXV, and vice-versa.

Inventions XVIII and any of inventions XXI and XXIV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the nucleic acid probe can be used to identify BACE1 genes in a library.

Inventions XIX and any of inventions XXI, XXIII and XXIV are mutually exclusive and independent. The kit comprising an antibody is not needed for any of inventions XXI, XXIII and XXVI, and vice versa.

Inventions XX and, inventions XXI and XXIV are mutually exclusive and independent methods. Invention XX required detection of peptide fragments, and inventions XXI and XXIV require detection of a polynucleotide. The protocols for detecting peptide fragments and polynucleotide are materially different and separate. Further, neither method is required for the other method.

Inventions XX, and inventions XXII and XXV are mutually exclusive and independent methods. Invention XX requires detecting Aβ11-40/42 peptide fragments and inventions XXII and XXV require the detection of BACE1 polypeptide. The means for detecting these unrelated proteins is materially different and separate. Further, invention XX and invention XXII are not required for the implementation of each other.

Inventions XX and XXIII are mutually exclusive and independent methods. The method of invention XX is to predict the therapeutic effectiveness of a compound comprising detecting Aβ11-40/42 fragments. The method of invention XXIII is to a method of monitoring the progression of Alzheimer's disease comprising measuring the accumulation of Aβ11-40/42 peptide fragments. The protocols for predicting treatment effectiveness, as in invention XX, and the protocols for monitoring the progression of Alzheimer's disease are materially different and separate. Further, neither method requires the other method for implementation.

Inventions XXI, and inventions XXII, XXIII and XXV are mutually exclusive and independent methods. The method for predicting the therapeutic effectiveness of a compound for treating Alzheimer's disease of invention XXI required determining the level of a BACE1 polynucleotide. Invention XXII, XXIII and XXV are to a method for predicting the therapeutic effectiveness of a compound for treating Alzheimer's disease and methods of monitoring the progression of Alzheimer's disease comprising measuring the accumulation of Aβ11-40/42 peptide. The protocols for measuring a BACE1 polynucleotide and Aβ11-40/42 peptide are materially different and separate. Further, the method of invention XXI is not needed to implement any of inventions XXII, XXIII and XXV.

Invention XXI and XXIV are mutually exclusive and independent methods. Both methods require the detection of BACE1 polynucleotide, but invention XXI is to predicting the therapeutic effectiveness of a compound for treating Alzheimer's disease, and invention XXIV is to monitoring the progression of Alzheimer's disease. Thus, the protocols are materially different and separate for the two methods. Neither method is needed to implement the other method.

Inventions XXII and XXIII are mutually exclusive and independent methods. Invention XXII requires the measurement of BACE1 polypeptide, and invention XXIII requires the measurement of Aβ11-40/42 peptide. As BACE1 and Aβ11-40/42 peptide are unrelated in amino acid sequence, the protocol for measuring them will be materially different and separate. Further, invention XXII is not required to implement invention XXIII and vice versa.

Inventions XXII and XXIV are mutually exclusive and independent methods. Invention XXII requires the measurement of BACE1 polypeptide, and invention XXIV requires the measurement of BACE1 polynucleotide. The protocols for measuring a BACE1 peptide are materially different and separate from the protocol for measuring a BACE1 polynucleotide. Further, invention XXII is not required to implement invention XXIV and vice versa.

Inventions XXII and XXV are mutually exclusive and independent methods. Invention XXII requires the measurement of BACE1 polypeptide to predict the effectiveness of a particular treatment. Invention XXV requires the measurement of BACE1 polypeptide to monitor the progression of Alzheimer's disease. The protocols determining treatment effectiveness are materially different and separate from protocols for monitoring Alzheimer's disease progression. Further, invention XXII is not required to implement invention XXV and vice versa.

Inventions XXIII and XXIV are mutually exclusive and independent methods. Invention XXIII requires the measurement of Aβ11-40/42 peptide. Invention XXIV requires the measurement of BACE1 polynucleotide. The protocols for measuring an Aβ11-40/42 peptide is materially different and separate from the protocol for measuring a BACE1 polynucleotide. Further, invention XXIII is not required to implement invention XXIV and vice versa.

Inventions XXIII and XXV are mutually exclusive and independent methods. Invention XXIII requires the measurement of Aβ11-40/42 peptide. Invention XXV requires the measurement of BACE1 polypeptide. The protocols for measuring an Aβ11-40/42 peptide are materially different and separate from the protocol for measuring a BACE1 polypeptide. Further, invention XXIII is not required to implement invention XXV and vice versa.

Inventions XXIV and XXV are mutually exclusive and independent methods. Invention XXIV requires the measurement of BACE1 polynucleotide. Invention XXV requires the measurement of BACE1 polypeptide. The protocols for measuring a BACE1 polynucleotide are materially different and separate from the protocol for measuring a BACE1 polypeptide. Further, invention XXIV is not required to implement invention XXV and vice versa.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 703-308-1126. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. R. Clark can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

Dr. D. Crouch
March 12, 2002